REMARKS

Upon entry of the present Amendment, claims 103, 107, 110-115, 118, 119, 121-124, 126-137 and 140-145 will be pending. Claims 1-102, 104-106, 108, 109, 116, 117, 120, 125, 138, 139 and 143 are withdrawn from consideration and/or canceled. Applicant reserves the rights to pursue the withdrawn and/or canceled subject matter in a subsequent application. Support for amended claim 103 for reciting "said gp55 antigen binds to an antibody produced by the hybridoma cell line CCTCC-C200305, said gp95 antigen binds to an antibody produced by the hybridoma cell line CCTCC-C200306, and said gp210 antigen binds to an antibody produced by the hybridoma cell line CCTCC-C200307, respectively" can be found throughout the application and, *inter alia*, in Example 2 at page 31, line 27 through page 32, line 7 of the present specification. Claims 107, 110-114, 118, 119, 121-124, 126, 128-133, 135, 136, 140 and 141 are amended to conform with the amendments of claim 103 and/or for other formality reasons. Support for new claim 144 for reciting "said primary T cell activation molecule is a MHC class I or a MHC class II molecule" can be found throughout the application and, *inter alia*, at page 9, lines 23-25 of the present specification. Support for new claim 145 for reciting "said costimulatory T cell activation molecule is selected from the group consisting of ICAM-1, ICAM-2, ICAM-3, LFA-1, LFA-2, VLA-1, VCAM-1, 4-1-BB L, B7-1 and B7-2" can be found throughout the application and, *inter alia*, at page 9, line 25 through page 10, line 2 of the present specification. The above-described amendments do not introduce any new matter into the present application.

Rejections under 35 U.S.C. § 112

Written description

Claims 103, 107, 110-115, 118, 119, 121-124, 126-137 and 140-143 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, the Examiner asserted that:

- the disclosure of an antibody to a protein of 55 kDa on the surface of one type of hepatocellular carcinoma cell line is insufficient to describe the genus as broadly claimed;
- as is the disclosure of four bridge molecules that is are all bispecific antibodies;
- as is the lack of disclosure of one or more primary or costimulatory T cell activation molecules on the surface of T cells of said patient mammal as a component of the claimed composition.

In the interests of advancing prosecution of the present application and without accepting the Examiner's assertion, applicant has amended the independent claim 103 to recite "said gp55 antigen binds to an antibody produced by the hybridoma cell line CCTCC-C200305, said gp95 antigen binds to an antibody produced by the hybridoma cell line CCTCC-C200306, and said gp210 antigen binds to an antibody produced by the hybridoma cell line CCTCC-C200307, respectively." It is respectfully submitted that the written description rejection based on the alleged insufficient description of gp55 antigen is rendered moot by the above amendment (*See Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 U.S.P.Q.2D (BNA) 1609 (Fed. Cir. 2002) holding that in light of the history of biological deposits for patent purposes, the goals of the patent law, and the practical difficulties of describing unique biological materials in a written description, reference in the specification to a deposit in a public depository, which makes its

contents accessible to the public when it is not otherwise available in written form, constitutes an adequate description of the deposited material sufficient to comply with the written description requirement of § 112, ¶ 1). The other two grounds for the written description rejection are also rendered moot by the amendments of claim 103.

Enablement

Claims 103, 107, 110-115, 118, 119, 121-124, 126-137 and 140-143 are rejected under 35 U .S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In particular, the Examiner asserted that the specification does not disclose how to make and/or use the instant invention on three grounds:

(1) making and using antibodies to any 55 kDa glycoprotein, i.e., "gp55", on the surface of any isolated autologous target autologous target carcinoma or lymphoma cells;

(2) making and using a composition comprising a bridge molecule that is not a bispecific antibody; and

(3) making and using a composition further comprising one or more primary or costimulatory T cell activation molecules on the surface of T cells in said patient mammal.

In the interests of advancing prosecution of the present application and without accepting the Examiner's assertion, applicant has amended the independent claim 103 to recite "said gp55 antigen binds to an antibody produced by the hybridoma cell line CCTCC-C200305, said gp95 antigen binds to an antibody produced by the hybridoma cell line CCTCC-C200306, and said gp210 antigen binds to an antibody produced by the hybridoma cell line CCTCC-C200307,

respectively." It is respectfully submitted that the enablement rejection based on the alleged insufficient teaching of gp55 binding antibody is rendered moot by the above amendment. The other two grounds for the non-enablement rejection are also rendered moot by the amendments of claim 103.

Indefiniteness

Claims 103, 107, 110-115, 118, 119, 121-124, 126-137 and 140-143 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner made the following specific rejections:

a. Claims 107, 114, 121-124, 126, 128 and 114 recite the limitation "said one or more hepatocellular carcinoma, lymphoma or colorectal carcinoma cells". There is insufficient antecedent basis for this limitation in the claim.

b. Claims 110-114 recite the limitation "said one or more CD28 or 4-1BB molecules". There is insufficient antecedent basis for this limitation in the claims.

c. Claims 112 and 113 recite the limitation "said one or more hepatocellular carcinoma, or colorectal carcinoma cells". There is insufficient antecedent basis for this limitation in the claim.

d. Claims 118, 128 and 131 recite the limitation "said one or more target hepatocellular carcinoma, lymphoma or colorectal carcinoma cells". There is insufficient antecedent basis for this limitation in the claim.

e. Claims 110-114, 130 and 132 recite the limitation "said one or more CD28 or 4-1BB molecules". There is insufficient antecedent basis for this limitation in the claim.

f. Claim 143 is indefinite in the recitation of "bridge molecule further comprises bispecific monoclonal antibody" because it is not clear what is meant, i.e., is the bridge molecule a bispecific monoclonal antibody? In addition, the article "a" appears to, be missing after "comprises".

g. Claims 129, 131 and 141 are indefinite in the recitation of antibodies which comprise "two or more" or "one or more" "antigen binding sites for one or more gp55 antigens on the surface of said one or more target hepatocellular carcinoma, lymphoma or colorectal carcinoma cells" or "one or more binding sties for antigen gp55" because the characteristics of the said gp55 antigens and hence, that of the said antibodies, are not known. The use of "gp55" as the sole means of identifying the protein to which the claimed antibody is specific renders the claim indefinite because "gp55" is merely a laboratory designation which does not clearly define the claimed product, since the said designation is merely a characterization of a protein by size and may refer to many different proteins.

It is respectfully submitted that these rejections are rendered moot by the amendments of claims 103, 107, 110-114, 118, 119, 121-124, 126, 128-133, 135, 136, 140 and 141.

It is respectfully submitted that the rejection of claims 103, 107, 110-115, 118, 119, 121-124, 126-137 and 140-143 under 35 U.S.C. § 112 is overcome by the above remarks and/or amendments and must be withdrawn.

CONCLUSION

Applicant submits that the rejections of claims 103, 107, 110-115, 118, 119, 121-124, 126-137 and 140-143 under 35 U.S.C. § 112 have been overcome by the above remarks and/or amendments. Early allowance of the pending claims 103, 107, 110-115, 118, 119, 121-124, 126-137 and 140-145 are earnestly requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing **532732000200**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: June 24, 2003

Respectfully submitted,

By: _____

Peng Chen
Registration No. 43,543

Morrison & Foerster LLP
3811 Valley Centre Drive
Suite 500
San Diego, California 92130-2332
Telephone: (858) 720-5117
Facsimile: (858) 720-5125

EXHIBIT A

中国典型培养物保藏中心

CHINA CENTER FOR TYPE CULTURE COLLECTION

中国 武汉 武汉大学 430072

http://www.cctcc.org or http://www.whu.edu.cn/cn/xjzd/cctcc/index.htm

电话：027－87682319 传真：027－87883833 Email:cctcc@whu.edu.cn

OUR REF.： 专利保藏 CCTCC-C200305

TO：02150805815

尊敬的郭亚军先生：

您好，谢谢您将生物材料保藏于本中心作专利目的。生物材料的相关信息如下：

1、培养物名称：抗小鼠肝癌细胞 gp55 单抗细胞株

保藏编号：CCTCC-C200305

收到日期：2003 年 6 月 10 日。

2、培养物名称：抗小鼠肝癌细胞 gp95 单抗细胞株

保藏编号：CCTCC-C200306

收到日期：2003 年 6 月 10 日。

3、培养物名称：抗小鼠肝癌细胞 gp210 单抗细胞株

保藏编号：CCTCC-C200307

收到日期：2003 年 6 月 10 日。

生物材料的存活检测正在进行之中，检测完成后，我们会发出保藏证明。按照专利法的规定，保藏证明最迟会在 10 月 10 日寄达您的手中。请将上述信息转告您的专利代理人。

另外，如果是职务发明，请告之我们申请人（单位）的详细中文名称。如果专利还要申请国际专利（PCT），请告诉我们申请人（单位）对应的英文名称。

30 年的保藏费与检测费共计 3600 元/株，请按附件指定的帐号汇入武汉大学，汇款寄出后请将银行回单通过传真或 EMAIL 给我们。

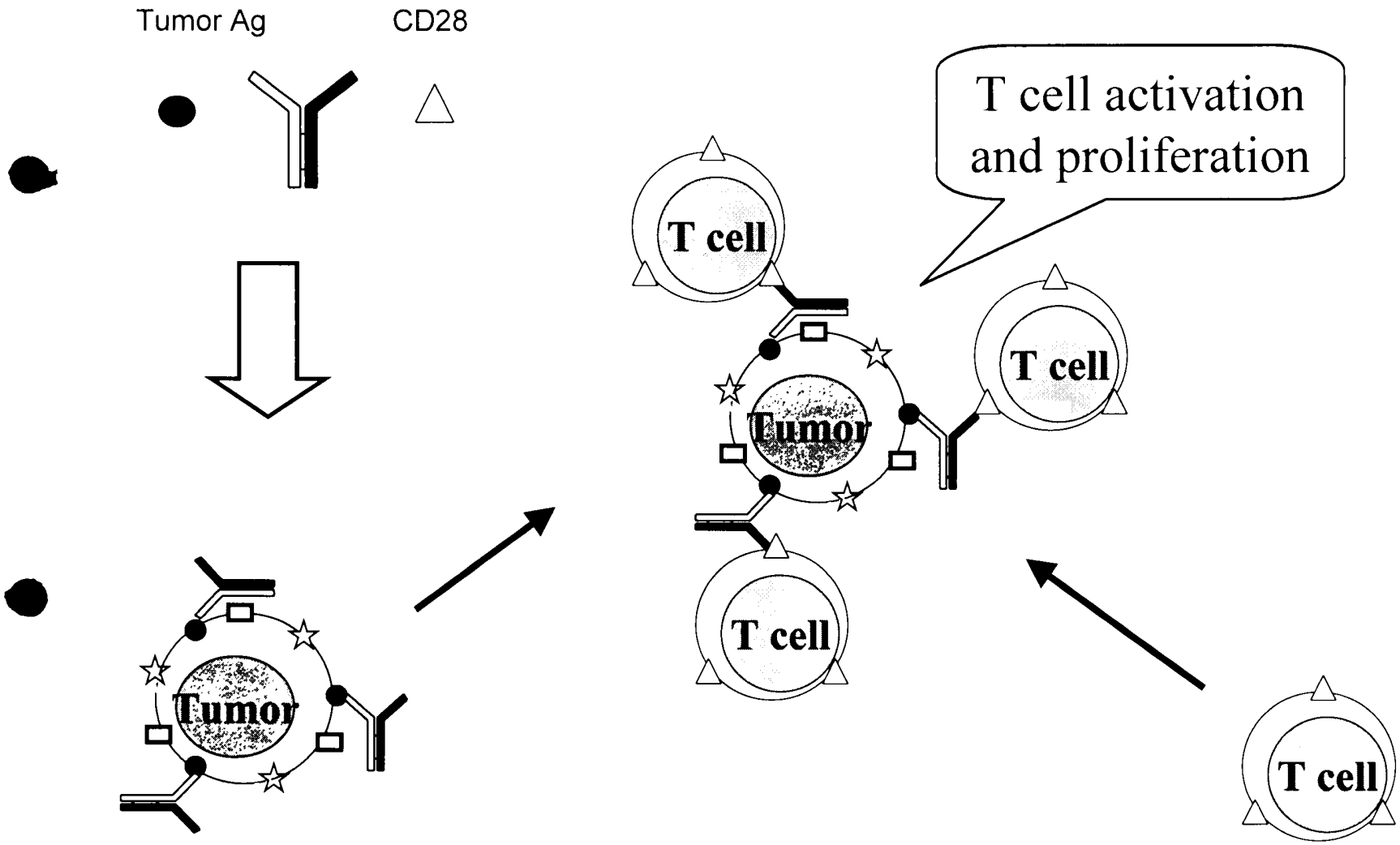
此致

敬礼

后三甫

CCTCC。

Inventive Scheme



Substantially isolated, pre-stimulated, pre-armed, purified tumor cells
(no or minimal free BsAb present)

Exhibit B

Fig 1

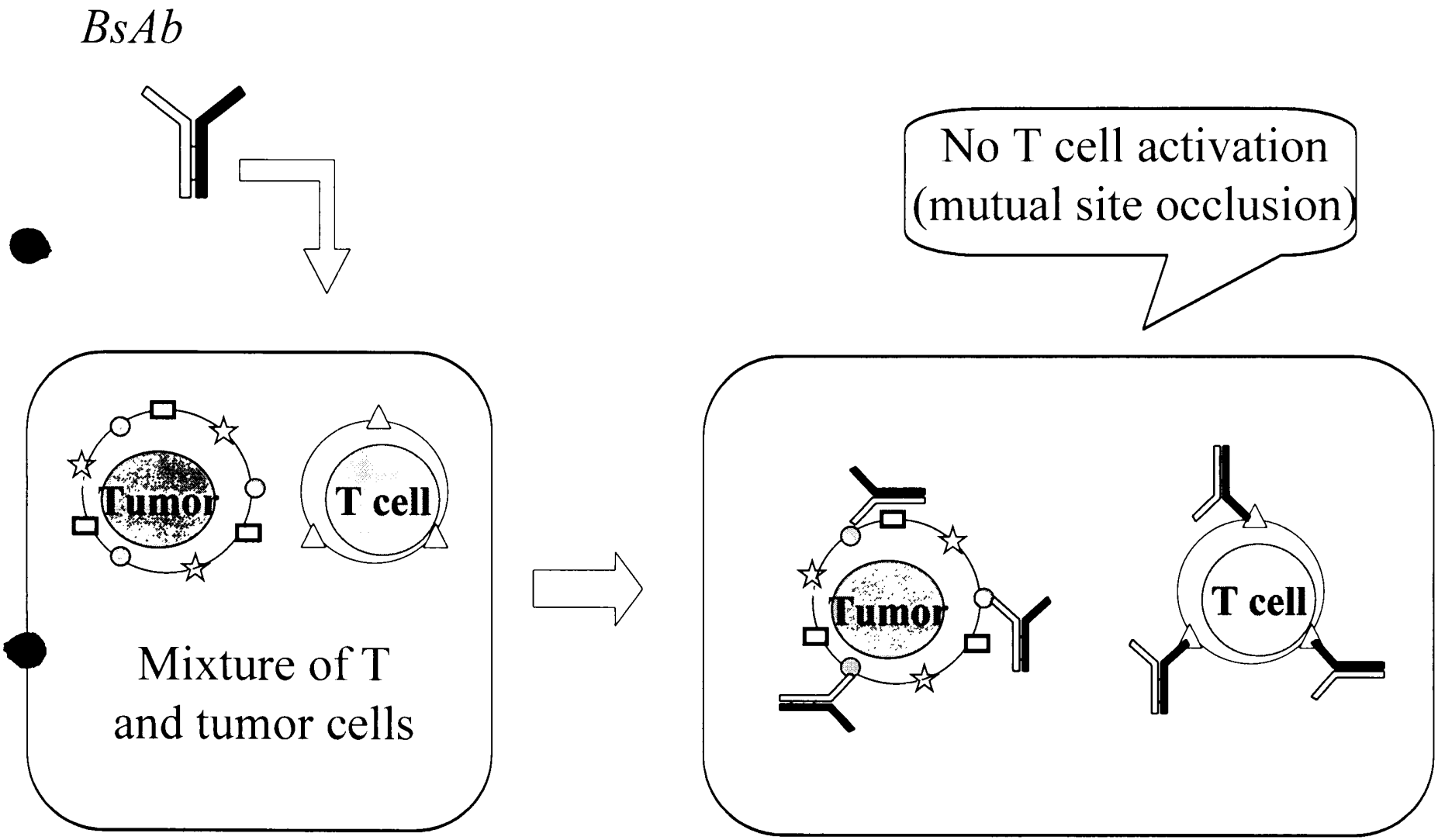

BsAb
No T cell activation
(mutual site occlusion)
Tumor
T cell
Mixture of T
and tumor cells
Tumor
T cell

Fig 2

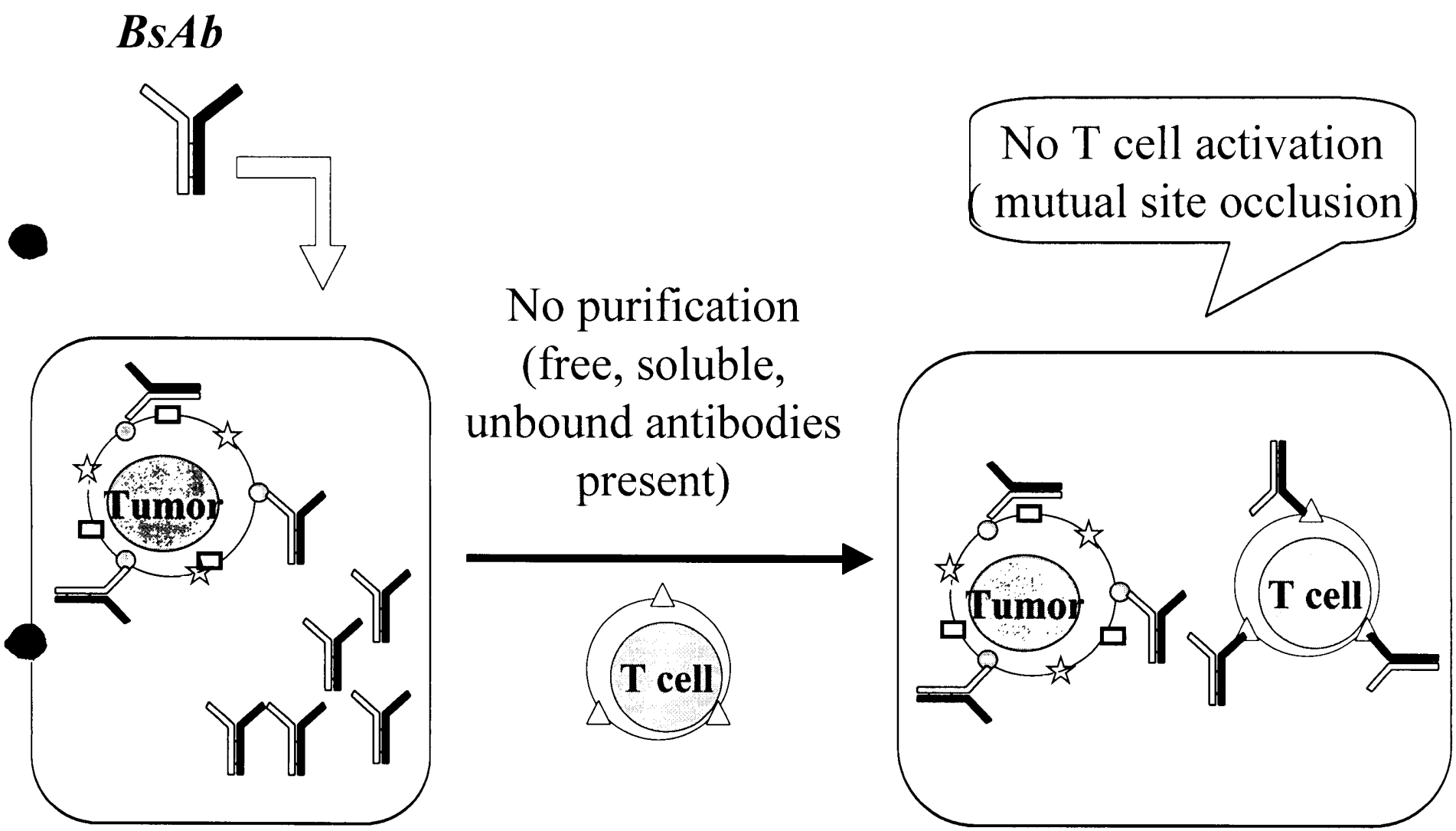

BsAb
Tumor
No purification
(free, soluble,
unbound antibodies
present)
T cell
No T cell activation
(mutual site occlusion)
Tumor
T cell

Fig 3

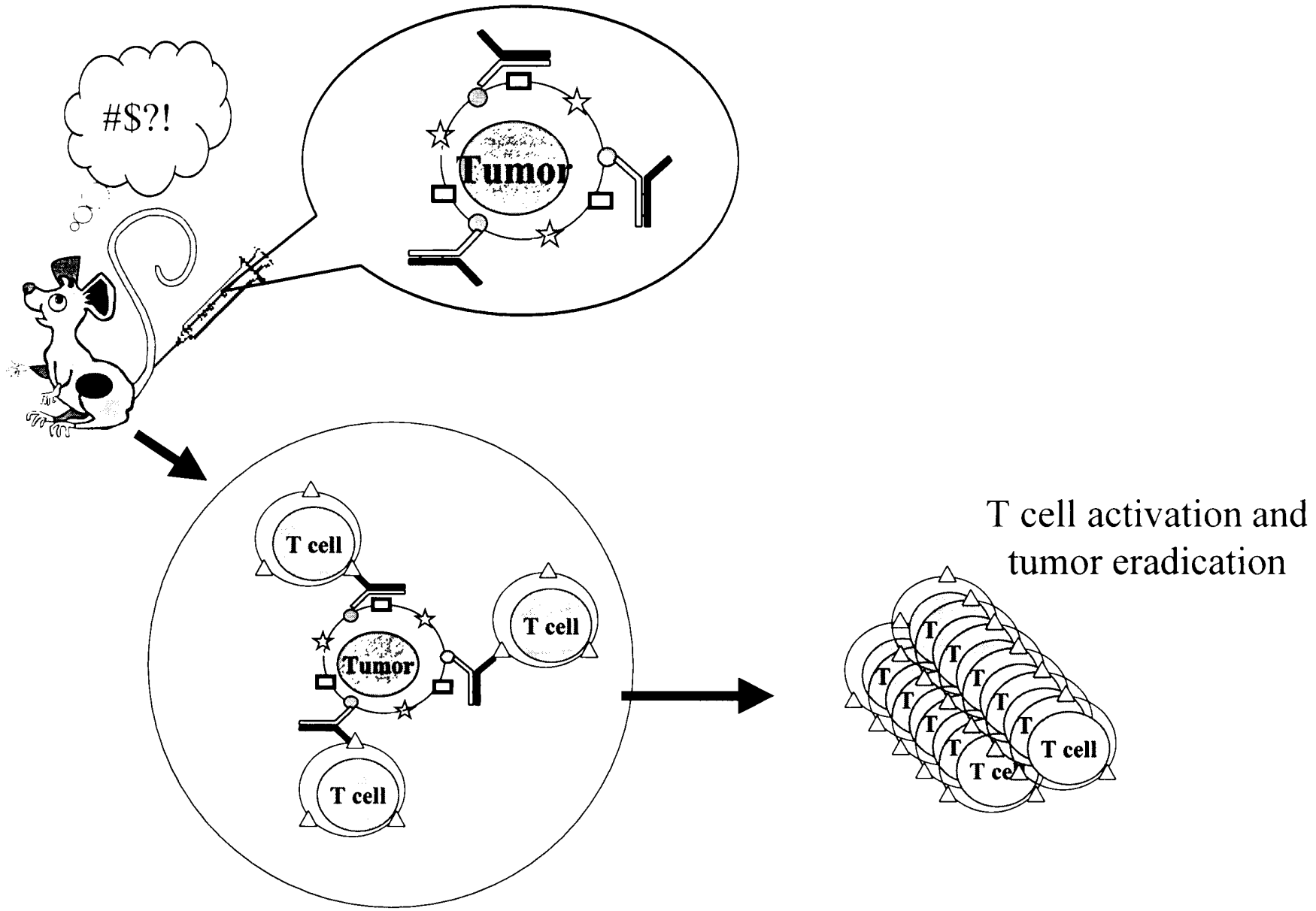

#$?!
Tumor
T cell
T cell
Tumor
T cell
T cell activation and
tumor eradication
T cell

Fig 4

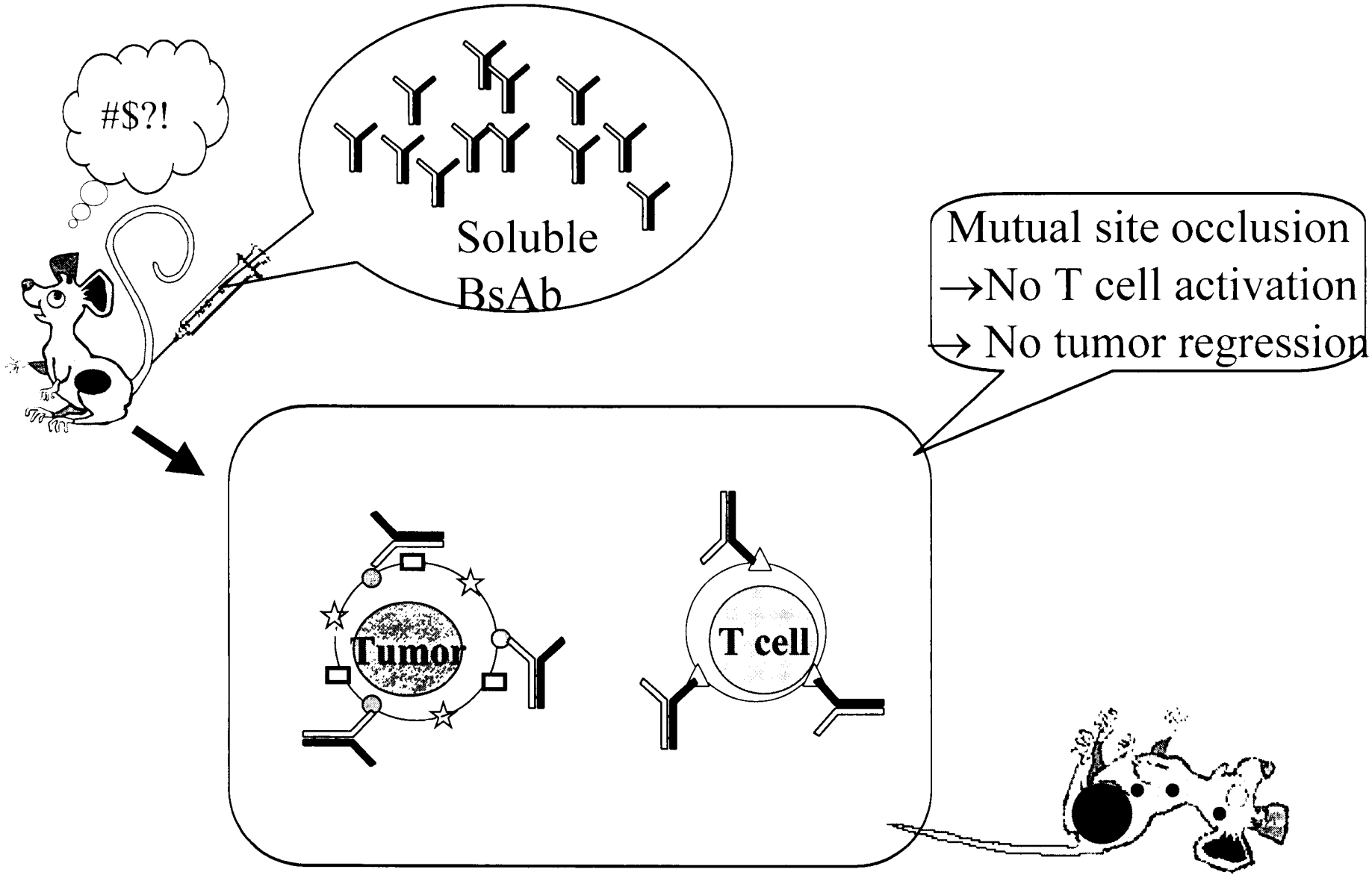

#$?!
Soluble
BsAb
Mutual site occlusion
→No T cell activation
→ No tumor regression
Tumor
T cell

Fig 5

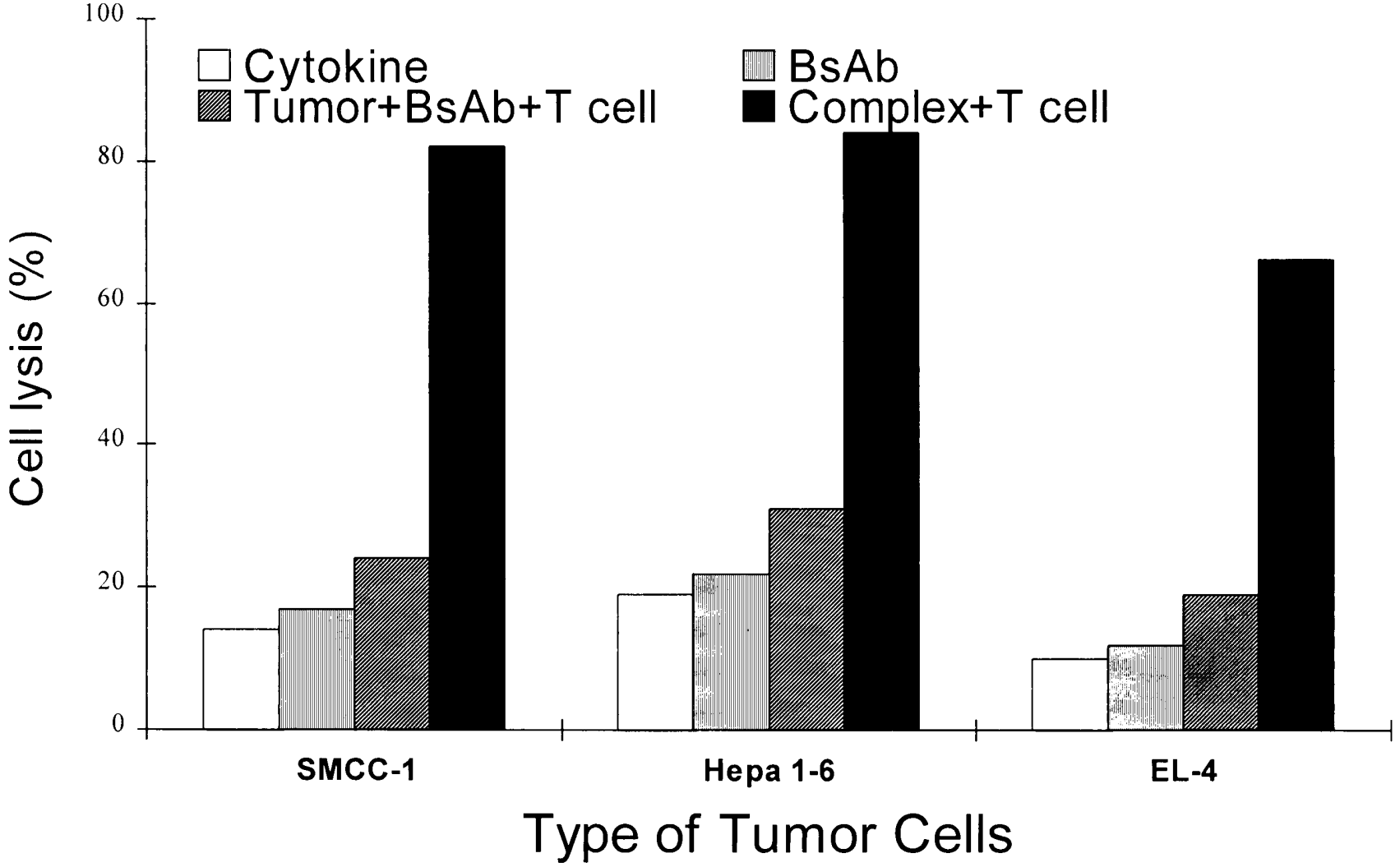

100
80
60
40
20
0
Cell lysis (%)
Cytokine
BsAb
Tumor+BsAb+T cell
Complex+T cell
SMCC-1
Hepa 1-6
EL-4
Type of Tumor Cells

Fig 6

Fig.1. Tumor cells were first treated with combination of cytokines and then co-cultured with BsAb (anti-tumor antigen and CD28 bi-specific monoclonal antibody) *in vitro*. Unbound BsAb was eliminated by purification. Cells armed with BsAb can activate T cells with generation of CTL mediated tumor immunity.

(● tumor antigen; △ CD28)

Fig. 2. Addition of BsAb into co-culture of tumor cells and T cells may form two distinct complexes, tumor×BsAb and T cell ×BsAb, which cannot thereafter bridge to each other.

Fig.3. When soluble (unbound) BsAb is co-administered with tumor cells, the free BsAb may selectively bind to CD28 on T cells and effectively block bridging.

Fig 4. The claimed vaccine when injected into a host can attract T cells, and activate them with generation of anti-tumor immune response.

Fig 5. No detectable anti-tumor immunity was obtained when cytokine treated tumor cells alone were subcutaneously injected, followed by intravenous injection of BsAb.

Fig 6. Only tumor:BsAb bridged complexes can stimulate naive T cells to generate CTLs.